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<p>(21) International Application Number: PCT/SE87/00240</p> <p>(22) International Filing Date: 13 May 1987 (13.05.87)</p> <p>(31) Priority Application Numbers: 8602242-3 8605456-6</p> <p>(32) Priority Dates: 16 May 1986 (16.05.86) 18 December 1986 (18.12.86)</p> <p>(33) Priority Country: SE</p> <p>(71) Applicant (for all designated States except US): OMEGA MEDICINTEKNIK AB [SE/SE]; Ernst Nilsson, Baggensgatan 19, S-111 31 Stockholm (SE).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only) : UNGER, Peter [SE/SE]; Värtavägen 35, S-115 29 Stockholm (SE). WESTBERG, Eric [SE/SE]; Rödstuguvägen 14, S-181 31 Lidingö (SE).</p>	<p>(74) Agent: NYBERG, Bengt; Carminger, Uusitalo & Nyberg Patentbyrå AB, P.O. Box 19055, S-104 32 Stockholm (SE).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), SU, US.</p> <p>Published With international search report. In English translation (filed in Swedish).</p>	
<p>(54) Title: METHOD AND APPARATUS FOR PLASMAPHERESIS</p> <p>(57) Abstract</p> <p>The method comprises withdrawal of a quantity of blood from a blood donor to an annular primary container (2) forming part of a closed flexible processing assembly positioned in a processing space provided in a centrifuge rotor and conformed to the processing assembly. During the withdrawal, the rotor is caused to perform an oscillating movement for agitating the blood whereupon the blood is centrifuged in the primary container to be separated into blood cells and plasma. While the centrifugation is going on the primary container is then compressed to expel the plasma fraction to a secondary container (3) positioned in the central region of the annular primary container. Liquid diluent is then fed to the primary container to resuspend the blood cell fraction while agitation is again accomplished by oscillating the rotor, whereupon the blood cell fraction is returned to the blood donor. The apparatus is a closed flexible processing assembly for use in carrying out the method according to the invention and comprises an annular primary container (2), a secondary container (3) positioned in the central region of the annular primary container, a collapsible connecting duct (7) connecting the portion of the primary container closest to the centre of rotation with the secondary container, and a flexible tube (4) connected to the primary container.</p>		

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Method and apparatus for plasmapheresis

This invention relates to a method and an apparatus for carrying out plasmapheresis.

Half of the blood is so-called plasma, a yellowish
5 liquid containing various proteins. The other half of the blood contains cellular material, such as red blood cells, white blood cells and platelets. Plasma is used in transfusions and as raw material for the pharmaceutical industry in connection with the production of pharmaceuticals, such
10 as albumin, gamma globulin and Factor VIII (haemophilia medicament).

Plasma may be obtained in pure form by centrifugation, about 200 ml of red blood cells and about 250 ml of plasma being obtainable from a donated blood unit of about
15 500 ml, including anticoagulant. The plasma fraction can also be obtained by plasmapheresis, in which the blood of the blood donor is withdrawn and centrifuged whereupon the red blood cells are returned to the donor. Plasmapheresis is advantageous because it is a cheaper method of obtaining
20 plasma in the case where red blood cells are not needed, because each withdrawal yields more plasma (in total 600 ml in the case of two-cycle plasmapheresis), and because plasmapheresis can be carried out more frequently than blood donation.

25 Relatively expensive automated equipment for plasmapheresis is known, such as the Haemonetic or Haemoscience machines which are made in the United States.

Apart from the high cost for the plasma production, these machines are only suitable for withdrawal in large
30 blood banks, and for that reason plasmapheresis has to be carried out manually in most cases, especially when withdrawal is carried out in mobile units.

When plasmapheresis is carried out manually, blood is withdrawn from a blood donor (BG) and conveyed through a
35 flexible tube to a bag positioned on a combined weighing scale and rocker. The scale discontinues the blood withdrawal and gives a warning when a sufficient amount of blood (about 450 ml) has been withdrawn, and the rocker mixes the blood with the anticoagulant. Thereupon the

flexible tube is cut off under the action of heat so that the ends of the flexible tube are sealed, and the bag is carried to a centrifuge in which separation takes place. In the next step the bag is transferred to a squeezing
5 device in which the plasma collected in the upper portion of the bag is expelled into a different bag. Saline is then added to the original bag containing the blood cells which are retransfused to the blood donor. Normally, this procedure is repeated with one and the same blood donor,
10 that is, so-called two-cycle plasmapheresis is carried out, yielding 500-600 ml of plasma, including the originally added anticoagulant.

This system has many disadvantages:

- Many manipulative steps including connections and
15 disconnections of flexible tubes are required;
- Separation of plasma from the centrifuged bag takes place manually and with the fractions held separated only under the action of the normal gravity, which means that high quality is not achieved, that
20 is, that cellular material is left in the plasma. In order that high quality may be achieved, it is necessary to carry out repeated centrifugations and to transfer the plasma to a further secondary bag, which means added costs;
- 25 - The method lends itself to confusion, because the bag is physically separated from the blood donor;
- The method is time-consuming in that it takes about one hour. It is easy to recruit persons for donating blood, which takes about 15 minutes, but it
30 is more difficult to find persons who can sacrifice one hour.

The object of the present invention is to provide a method and an apparatus permitting small-scale semi-automated utilization of plasmapheresis, e.g. in mobile
35 units, such as blood buses, and having the following advantages over manual plasmapheresis:

- Increased speed;
- Improved plasma quality (fewer cells left in the plasma);

- Simplified procedure and reduced number of manipulative steps.

- Increased safety because of reduced danger of confusion;

- 5 - A large stationary centrifuge can be dispensed with.

This object is achieved by a method and an apparatus as defined in the claims.

When carrying out the method according to the invention,
10 a centrifuge of the type described in Swedish patent application No. 8602242-3 may be used. This patent application discloses a centrifuge in which the processing space
of the rotor includes an annular separation compartment and a central compartment. The volume of the separation
15 compartment can be reduced during the centrifugation to displace a centrifugally separated component into the central compartment. An oscillating reciprocary movement can be imparted to the rotor, and the processing space can be subjected to overpressure or vacuum.

20 When carrying out the method according to the present invention, blood is withdrawn from the blood donor direct into an annular primary container forming part of a closed flexible processing assembly which is positioned in the processing space of the centrifuge rotor. The centrifuge
25 may be positioned immediately adjacent the blood donor coach. During the withdrawal the rotor is oscillated to mix the blood with anticoagulant with which the primary container has been primed beforehand or which is supplied at the same time as the blood. The next step consists in
30 centrifugation of the blood in the primary container to separate blood cells and plasma. After a given centrifuging time, the plasma is expelled to a secondary container forming part of the processing assembly and disposed in the central region of the annular primary container. This
35 transfer of the plasma may preferably be effected by increasing the rotational speed of the centrifuge so that a centrifugally operated valve opens a connecting duct between the primary container and the secondary container and at the same time subjecting the primary container to a

squeezing pressure. Thereupon the centrifugation is discontinued, and liquid diluent (physiological saline) is fed to the primary container while agitation is again effected by oscillating the rotor, and the thus resuspended blood cell fraction is retransfused to the blood donor.

The invention also relates to a closed flexible processing assembly for use in carrying out the method. The processing assembly comprises an annular primary container, a secondary container positioned in the central region of the annulus, and a closable connecting duct between the portion of the primary container closest to the centre of rotation and the secondary container, and a flexible tube connected to the primary container for supply of blood to the processing assembly and withdrawal of blood cell suspension from the processing assembly.

The invention will be described in greater detail hereinafter with reference to the accompanying drawings, in which:

Fig. 1 is an elevational view of one embodiment of a processing assembly according to the invention;

Fig. 2 is a plan view of the processing assembly;

Fig. 3 is a diagrammatical cross-sectional view of the centrifuge rotor according to SE 8602242-3;

Figs. 4a-4e show the various steps of the method according to the invention.

Figs. 1 and 2 show a processing assembly 1 comprising an annular primary container 2 and a secondary container 3 in the centre of the annulus. A flexible tube 4 is connected to the primary container, passes through a sealing body 5 and ends in a sterile connector 6. A collapsible flexible tube 7 connects the portion of the primary container 2 closest to the centre of rotation with the secondary container 3. The flexible tube 7 is provided with a check valve 21 which permits liquid flow from the primary container to the secondary container but closes to flow in the opposite direction. The flexible tube 7 is also passed through the sealing body 5 and forms a loop 8 on its outer side and then returns through the sealing body. The sealing body 5, which may consist of a rubber

stopper, for example, serves to seal the separation space of the rotor from the surrounding atmosphere after the processing assembly has been brought in position in the separation space.

5 The processing assembly can be made from pieces of plastic foil which are interconnected by an outer annular joint 9 and an inner annular joint 10. In this way, an annular primary container 2 and a disc-like secondary container 3 in the central region of the annulus are
10 formed. Suitably, the inner joint is provided with a perforation 11 in the middle so that the containers can be disconnected from one another. The plastic foil preferably is made of PVC or polyethylene, and the joining can be effected by heat sealing in well-known manner. The flexible
15 tubes 4 and 7 are welded in similar manner to the plastic sheet, if desired with a reinforcing neck at the point of attachment.

 Fig. 3 is a diagrammatic cross-section of a rotor which is suitable for use in carrying out the present
20 invention. A centrifuge rotor of the illustrated design is described in greater detail in Swedish patent application No. 8602242-3. The processing assembly 1 is positioned in the processing space 12, 13 of the rotor. Numeral 12 designates an annular separation compartment and numeral
25 13 designates a central compartment communicating with the separation compartment. In the cover 14 of the rotor there is an opening 15 above the central compartment. When the processing assembly has been brought in position in the rotor, this opening is sealed by pulling the sealing body
30 5 upwardly into the opening 15 whereupon the processing space of the rotor may be subjected to overpressure or vacuum by way of a connection 16. When this is done, the valved connector 6 of the flexible tube 4 and the tube loop 8, which is inserted in a centrifugally operated
35 pinch valve 17, are positioned outside the sealed separation space. A pressure medium 18, e.g. a rubber body, is deformed as a result of the centrifugation and exerts a pressure on the primary container 2 positioned in the

separation compartment 12. The rotor is driven by a programme-controlled motor (not shown).

In use of the apparatus of Figs. 1 and 2, a processing assembly is positioned in the rotor, and the processing space of the rotor is sealed by means of the sealing body 5. The tube loop 8 is inserted in the pinch valve 17. Figs. 4a-4e show the various steps of the procedure which is then carried out.

Fig. 4a shows withdrawal of blood during agitation. The connector 6 is attached to a standard withdrawal kit which is also linked to a blood donor (BG). Blood is withdrawn from the blood donor and at the same time anticoagulant (CPD) is added. Alternatively, if only single-cycle plasmapheresis is to be carried out, the primary container may be primed with anticoagulant beforehand. When two-cycle plasmapheresis is carried out, anticoagulant is continuously supplied through the blood withdrawal kit as shown in Fig. 4 or by priming the primary container with one unit of anticoagulant. If the negative hydrostatic pressure from the blood donor to the primary container is insufficient for normal withdrawal of blood, the processing space of the centrifuge may be subjected to vacuum. In the centrifuge according to SE 8602246-3 a vacuum pump is connected to the passage 16 (Fig. 3) to provide the desired increased vacuum. The blood of the donor now flows into the primary container 2. To ensure that the anticoagulant is thoroughly mixed with the blood, the centrifuge is programmed during this phase to oscillate the rotor at a predetermined amplitude and a predetermined frequency.

The primary container suitably is designed to accommodate a blood donation (usually 500 ml) so that the withdrawal of the blood is discontinued automatically when this quantity has been withdrawn. The centrifuge may be equipped with an alarm device which is activated when the primary container has been filled. Attention is thereby called to an attendant who disconnects the blood withdrawal kit from the connector 6, and in the customary manner saline is fed to the blood donor to replace a

portion of the withdrawn blood and to keep the blood withdrawal tubes clean. At the same time, the centrifuging step I (Fig. 4b) is initiated by switching the centrifuge from oscillation to rotation, and the rotor is accelerated to a selected separation speed. In centrifuging step I the blood cells settle in the peripheral part of the primary container while the plasma is collected in the portion of the annulus 2 closest to the centre. In this step the connecting tube 7 is kept closed by the centrifugal valve 17, for example.

After a calculated time has elapsed, centrifuging step II (Fig. 4c) is initiated. In this step the separated plasma is caused to flow to the secondary container 3 by way of the check valve 21. This is accomplished by reducing the volume of the separation compartment while the centrifugation is going on so that the primary container 2 is compressed and the plasma fraction is displaced to the secondary container 3. In one embodiment of the centrifuge described in SE 8602242-3, this is done with the aid of a rubber body 18 (Fig. 3) positioned in the rotor, which rubber body has greater density than the blood and/or is acted on by radially displaceable weight segments. During the centrifugation the rubber body exerts a pressure on the primary container in the separation compartment. However, the centrifuged blood volume cannot move, because the valve 17 is closed. While centrifuging step II is carried out, the valve 17 is opened and the rubber body 18 is deformed into the separation compartment and expels a corresponding volume of plasma into the secondary container. In accordance with a preferred embodiment, centrifuging step II is carried out at a higher centrifuge speed than centrifuging step I. The transfer of the plasma then takes place while the separated phases are subjected to the action of a centrifugal field which is even stronger than that existing during the settling phase (centrifuging step I). The danger of resuspending blood cells in the plasma fraction during the transfer therefore is very small. When two centrifuge speeds are used, the valve 17 may be a centrifugal valve set to be closed at the lower speed and

to open at the higher speed. The rubber body 18 and the weight segments or corresponding means may also be adapted to provide the required transfer pressure only when the higher speed has been reached.

5 The transfer may also be monitored by photocells, e.g. at the tube loop 8, which then has to be transparent. If cells reach the light path of the photocell, the transfer is discontinued, e.g. by reducing the centrifuge speed so that the centrifugal valve 17 closes and/or the pressure
10 action of the rubber body ceases.

After a predetermined time has elapsed, the centrifuge is stopped and the resuspension step is initiated (Fig. 4d). Liquid diluent (physiological saline) is now fed to the primary container by way of the connector 6 while the
15 rotor is again oscillated. The processing space of the centrifuge may then be subjected to vacuum in the same way as during the withdrawal of blood so that the introduction of the saline into the primary container is facilitated. When the cell concentrate remaining in the primary container
20 has been diluted to the desired concentration, the retransfusion step (Fig. 4e) is commenced. A new flexible tube is attached to the connector 6, and the processing space on the rotor is subjected to a predetermined overpressure, e.g. by pumping air into it by way of the passage 16. The
25 contents of the primary container then flow through the attached flexible tube by way of an air trap and a connected transfusion kit with a filter and back to the blood donor. When the primary container 2 is empty, a single-cycle plasmapheresis is completed. When two-cycle plasmapheresis
30 is carried out, the secondary container 3 is made large enough to accommodate two batches of plasma, and the procedure is repeated with the same processing assembly. The cover 14 is then removed, and the flexible tube 7 is sealed and cut, e.g. by means of a pair of heat-sealing
35 jaws. The secondary container with the recovered plasma is torn away from the primary container along the perforation 11 of the joint 10. Then the secondary container can immediately be frozen to save the quality of the plasma.

Claims

1. Method for carrying out plasmapheresis, characterised in that

5 a quantity of blood is withdrawn from a blood donor to an annular primary container (2) forming part of a closed flexible processing assembly (1) positioned in a processing space (12,13) in the rotor of a centrifuge, said processing space being conformed to the processing assembly;

10 during the withdrawal the rotor is caused to perform an agitating movement for agitation of the blood;

the blood is centrifuged in the primary container to be separated into blood cells and plasma;

15 during the centrifugation the primary container is compressed to expel the plasma fraction to a secondary container (3) disposed in the central region of the annular primary container;

liquid diluent is fed to the primary container for resuspending the blood cell fraction while agitation is carried out again by oscillating the rotor, and

20 the blood cell fraction is returned to the blood donor.

2. Method according to claim 1, characterised in that the blood is centrifuged at a first speed with a collapsible connecting duct (7) between the primary container and the
25 secondary container being closed and in that the rotational speed of the rotor is then increased to a second rotational speed at which the connecting duct is open.

3. Method according to claim 1, characterised in that the processing space (12,13) of the rotor is subjected to
30 vacuum during the withdrawal of blood to the primary container.

4. Method according to claim 1, characterised in that the processing space (12,13) of the rotor is pressurized during the returning of the blood cells to the blood
35 donor.

5. A closed flexible processing assembly for use in carrying out the method according to any of claims 1 to 5, characterised by an annular primary container (2); a secondary container (3) positioned in the central region

of the annular primary container; a collapsible connecting duct (7) connecting the portion of the primary container closest to the centre of rotation with the secondary container; and a flexible tube (4) connected to the
5 primary container.

6. A processing assembly according to claim 5, characterised by a sealing body (5) for sealing the processing space (12,13) of the rotor from the surrounding atmosphere after the processing assembly has been posi-
10 tioned in said space with the flexible tube (4) accessible from outside.

7. A processing assembly according to claim 6, characterised in that the collapsible connecting duct between the primary container and the secondary container
15 comprises a flexible tube extending through the sealing body (5) so as to form a loop (8) exteriorly of the sealing body.

8. A processing assembly according to claim 5, characterised in that the connecting duct (7) includes a
20 check valve (21) permitting liquid flow from the primary container to the secondary container.

9. A processing assembly according to claim 5, characterised in that the primary and secondary containers consist of pieces of plastic foil joined together by an
25 outer annular joint (9) and an inner annular joint (10).

10. A processing assembly according to claim 9, characterised in that the inner annular joint (10) is perforated so that the containers can be disconnected from one another.
30

1 / 2

Fig. 1

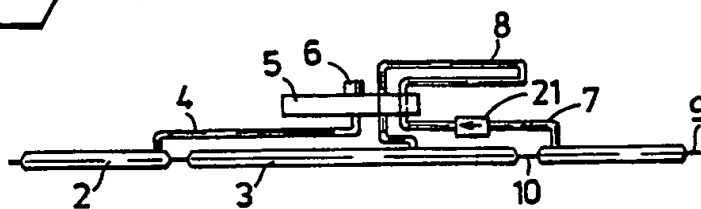


Fig. 2

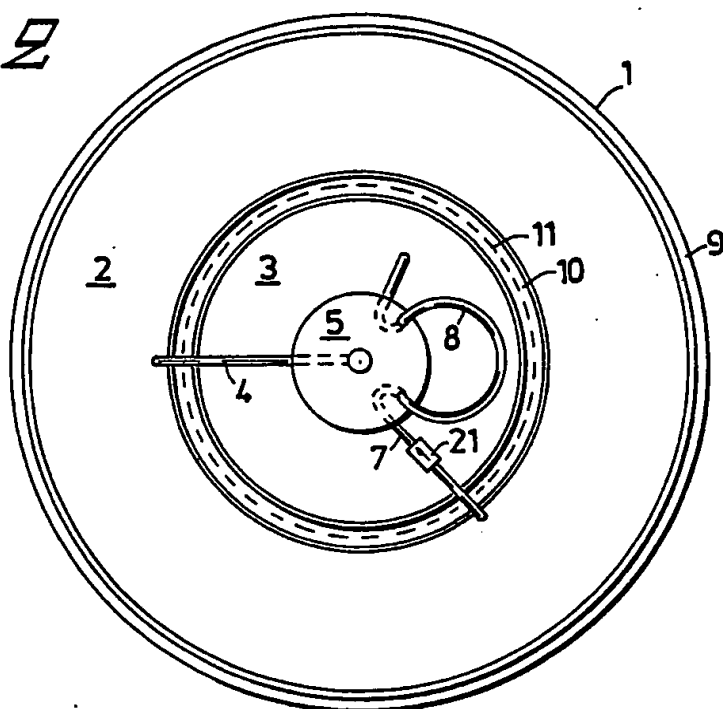
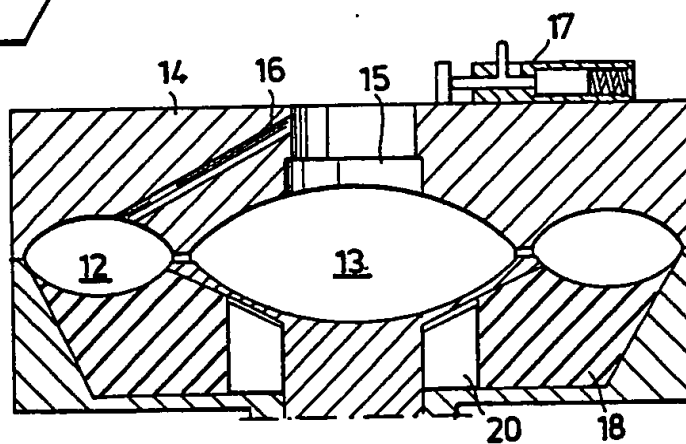


Fig. 3

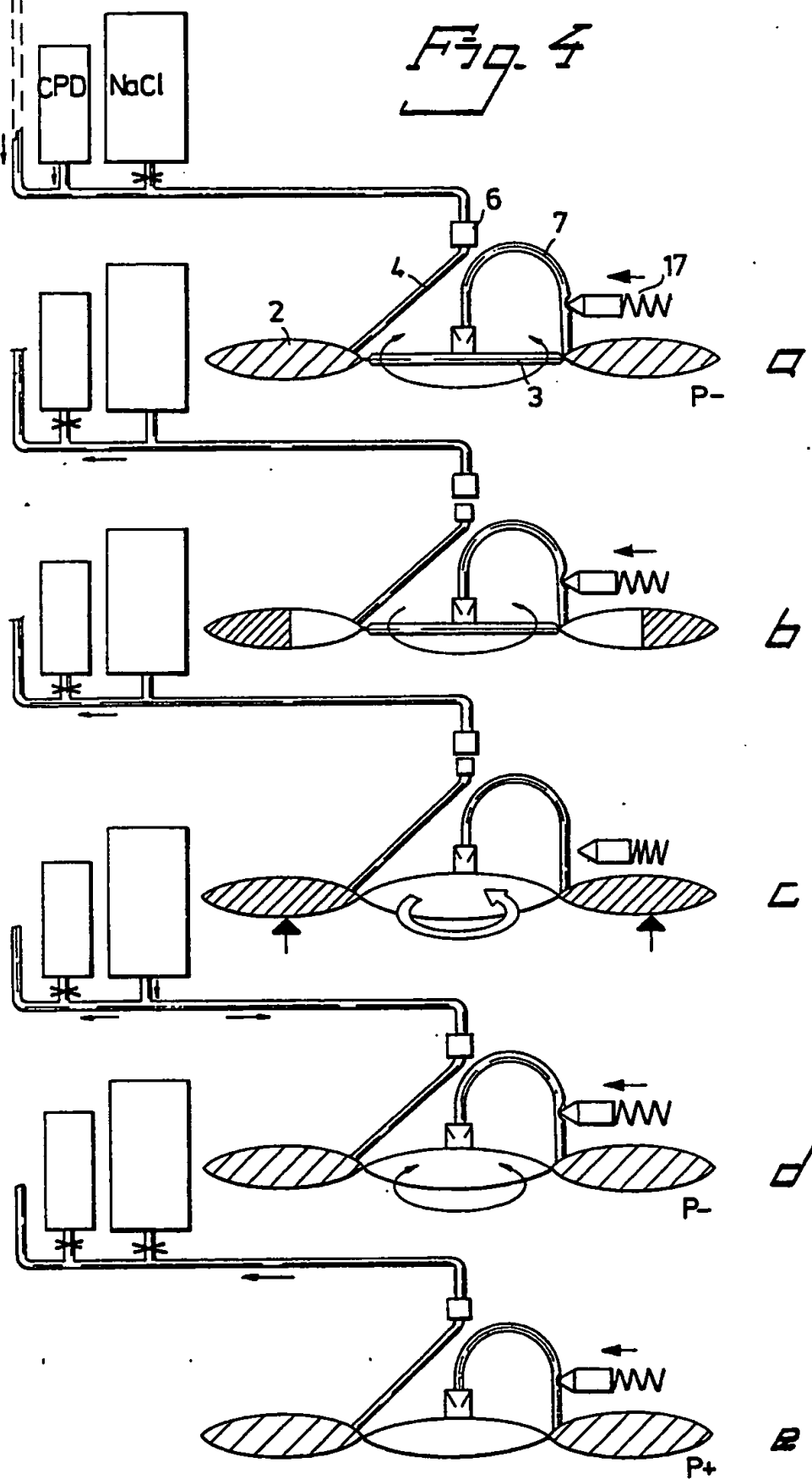


SUBSTITUTE SHEET

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Blood donor

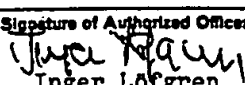
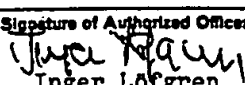
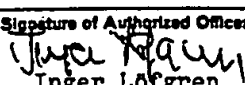
Fig. 4



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INTERNATIONAL SEARCH REP RT

International Application No PCT/SE87/00240

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC ⁴ <div style="text-align: center; padding: 5px;">A 61 M 1/36</div>														
II. FIELDS SEARCHED <div style="text-align: center; padding: 5px;">Minimum Documentation Searched ⁷</div> <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 20%; padding: 5px;">Classification System</th> <th style="padding: 5px;">Classification Symbols</th> </tr> <tr> <td style="padding: 5px;">IPC 4</td> <td style="padding: 5px;">A 61 M 1/34, /36; B 04 B 5/00-/04, 11/00-/04, 15/00</td> </tr> <tr> <td style="padding: 5px;">US C1</td> <td style="padding: 5px;">128:214R; 210:782; 233:3, 14, 19, 27, 28, 46, 47; 494:1-85; 604:4-6</td> </tr> </table> <div style="text-align: center; padding: 5px;">Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸</div> <div style="padding: 10px;">SE, NO, DK, FI classes as above</div>			Classification System	Classification Symbols	IPC 4	A 61 M 1/34, /36; B 04 B 5/00-/04, 11/00-/04, 15/00	US C1	128:214R; 210:782; 233:3, 14, 19, 27, 28, 46, 47; 494:1-85; 604:4-6						
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III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; padding: 5px;">Category ⁹</th> <th style="width: 60%; padding: 5px;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 30%; padding: 5px;">Relevant to Claim No. ¹³</th> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">US, A, 4 303 193 (HAEMONETICS CORPORATION) 1 December 1981 & EP, 0014093 WO, 80/01470 EP, 0023220 US, 4285464 CA, 1147308</td> <td style="text-align: center; vertical-align: top; padding: 5px;">1, 5-6</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">US, A, 3 244 363 (GEORGE HEIN, SAN CARLOS) 5 April 1966</td> <td style="text-align: center; vertical-align: top; padding: 5px;">5-6</td> </tr> <tr> <td style="text-align: center; vertical-align: top; padding: 5px;">X</td> <td style="padding: 5px;">SE, B, 354 582 (AGA AB) 19 March 1973</td> <td style="text-align: center; vertical-align: top; padding: 5px;">5-6</td> </tr> </table>			Category ⁹	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	US, A, 4 303 193 (HAEMONETICS CORPORATION) 1 December 1981 & EP, 0014093 WO, 80/01470 EP, 0023220 US, 4285464 CA, 1147308	1, 5-6	X	US, A, 3 244 363 (GEORGE HEIN, SAN CARLOS) 5 April 1966	5-6	X	SE, B, 354 582 (AGA AB) 19 March 1973	5-6
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<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>														
IV. CERTIFICATION <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> Date of the Actual Completion of the International Search <div style="text-align: center; padding: 5px;">1987-07-28</div> </td> <td style="width: 50%; padding: 5px;"> Date of Mailing of this International Search Report <div style="text-align: center; padding: 5px;">1987-08-04</div> </td> </tr> <tr> <td style="padding: 5px;"> International Searching Authority <div style="text-align: center; padding: 5px;">Swedish Patent Office</div> </td> <td style="padding: 5px;"> Signature of Authorized Officer <div style="text-align: center; padding: 5px;">  Inger Löfgren </div> </td> </tr> </table>			Date of the Actual Completion of the International Search <div style="text-align: center; padding: 5px;">1987-07-28</div>	Date of Mailing of this International Search Report <div style="text-align: center; padding: 5px;">1987-08-04</div>	International Searching Authority <div style="text-align: center; padding: 5px;">Swedish Patent Office</div>	Signature of Authorized Officer <div style="text-align: center; padding: 5px;">  Inger Löfgren </div>								
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